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Opportunistic infections and AIDS malignancies early after initiating combination antiretroviral therapy in high-income countries

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Redefining the HIV epidemic in Nigeria: from national to state level

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Background: Governments are increasingly recognizing the need to focus limited HIV resources on specific geographic areas and specific populations to have a greater impact. Nigeria, with the second largest HIV epidemic in the world, is an important example of where more localized programming has the potential to improve the efficiency of the HIV response.

Methods: Using Spectrum software we modelled the Nigerian HIV epidemic using two methods: First, we created national HIV estimates using trends in urban and rural areas. Second, we created national HIV estimates using trends from each of the 37 states in Nigeria and aggregated these results. In both instances we used HIV surveillance data from antenatal clinics and household surveys and aggregated the trends to determine the national epidemic.

Results: The state models showed divergent trends in the 37 states. Comparing the national results calculated from the two methods resulted in different conclusions. In the aggregated state files, adult HIV incidence in Nigeria was stable between 2005 and 2013 (change of -6%), whereas the urban and rural file suggested incidence was decreasing over the same time (change of -50%). This difference was also reflected in the HIV prevalence trends, although the two methods showed similar trends in AIDS-related mortality. The two models had similar adult HIV prevalence in 2013: 3.0% ($2.0-4.5\%$) in the aggregated state files versus 3.2% ($3.0-3.5\%$) in the urban/rural file.

Conclusion: The state-level estimates provide insight into the variations of the HIV epidemic in each state and provide useful information for programme managers. However, the reliability of the results is highly dependent on the amount and quality of data available from each sub-national area.

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Introduction

Globally, there is an increased interest in understanding the HIV epidemic at the sub-national level and to distinguish the geographic distribution of the HIV epidemic and the response within those sub-national areas. Hypothetically, if programme managers know more precisely where new infections are taking place or where AIDS-related deaths are occurring, they can target their responses more accurately [1].

A sub-national perspective is of particular importance in Nigeria, given the country's high HIV prevalence, large population and hence large numbers of people living with HIV (second largest in the world), wide geographic spread with many culturally diverse states, and marked differences in HIV infection across the geographic locations [2,3]. Hence, there is an immediate need to prioritize the country's HIV response to maximize the impact, given the limited resources allocated to HIV in the country and in the face of dwindling external

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resources for the HIV response. Currently, domestic spending on HIV programmes accounts for a little over 20% of the HIV expenditure on the response [4]. Substantial emphasis must be placed on state-level programming to effectively prioritize available resources, increase ownership of the response, and to ensure improved access and sustainability.

Sub-national surveillance data and HIV estimates are needed to monitor the diverse epidemics. Early in the HIV epidemic, surveillance experts recognized that there were differences in the HIV epidemic between the urban and the rural areas [5,6]. The urban and rural areas were considered to represent different epidemic zones within a country. As a result, surveillance guidance proposed monitoring HIV prevalence trends separately in urban and rural areas, and surveillance systems within antenatal clinics (ANCs) were set up accordingly [7].

As surveillance systems have evolved, it has become increasingly evident that the urban and rural areas do not necessarily represent unique epidemic zones in all countries. Epidemic zones often vary by geographic areas. For example, in Namibia and Botswana, there is little difference in the HIV prevalence from ANC attendees in the urban and rural areas, whereas there are large differences in ANC HIV prevalence by region within the country [8,9]. In Nigeria, the difference between the urban and the rural areas is also small, with estimated prevalence among persons 15–64 years in urban areas of 3.2% and in rural areas of 3.6% [10]. The direction of trends varies considerably by city in Nigeria, suggesting that combining all urban data into a single trend should be approached with a degree of caution. Similarly, not all rural areas in Nigeria show the same HIV prevalence trends [11].

Whereas it is evident that sub-national estimates are needed, a key question remains: Can we derive a more accurate understanding of the national HIV epidemic by monitoring trends within states instead of monitoring trends in the urban and rural areas? In this study, we describe the results of creating HIV estimates for Nigeria using state-specific trends compared to using urban and rural trends, and discuss the variation in the results and implications for other countries creating sub-national estimates.

Methods

UNAIDS recommends that countries use the Spectrum software to create national HIV estimates. Nigeria has produced national HIV estimates using Spectrum for over 10 years using urban and rural trends.

For the purposes of this analysis, we reviewed national estimates of HIV prevalence and incidence among adults

(15–49 years) and AIDS-related mortality among all ages based on a model developed from prevalence trends in urban and rural areas and the aggregated results from 37 state models developed from state trends. The state files were not divided by urban and rural areas due primarily to the small number of sites in each state and minimal differences by urban and rural areas [11].

Spectrum software

The Spectrum computer package is comprised of a number of modules. The backbone of Spectrum is the demographic module against which all estimates are produced. The demographic projection module in Spectrum includes data on population by sex and age from 1970 through 2030. Corresponding data on fertility, non-AIDS mortality and migration are also included in the model. The demographic data are drawn from the United Nations Population Division World Population Prospects 2012 edition. The United Nations Population Division produces fertility, mortality and migration projections for the country of Nigeria, but does not produce sub-national projections.

The demographic data required for each model include the population by 5-year age group and sex for the year 1970. From 1970 until the end of the projection, the software progresses the population forward based on demographic indicators on fertility, mortality, and migration.

The AIDS impact module in Spectrum is the module that produces the estimates specific to HIV [12]. Input data required for this module in a generalized HIV epidemic setting include HIV prevalence from ANC surveillance and surveys, program data on the numbers of adults and children on antiretroviral therapy (ART) and the number of HIV-positive pregnant women receiving antiretroviral medicines to prevent vertical transmission by regimen. Trends in HIV prevalence are estimated from surveillance among women at antenatal clinics and trends from the general population in household surveys. The trends are calibrated to match the level of HIV prevalence found among the general population in household surveys. Using the data on HIV prevalence and adjusting for the number of deaths (given the number of people receiving ART), trends in incidence are calculated using the Estimations and Projections Package within Spectrum. The incidence trends are used to calculate the key variables that describe the impact of HIV on the population.

For the urban/rural model, separate prevalence trends were fit for urban and rural areas and then combined into single national prevalence and incidence trends based on the distribution of the population between urban and rural areas. Calculation of other demographic and HIV variables occurs for the entire national population.

For the state files, national mortality and fertility rates were used for the initial part of the model. After 2008, the demographic variables were adjusted to reflect fertility and mortality data from the Demographic and Health Surveys conducted in 2008 and 2013 (these are different than the surveys mentioned below and did not contain HIV testing). In addition, the rates of population growth from the National Population Bureau were used to inform the population size between the 2006 census and 2013. Thus, for recent years, each state file reflects the state-specific fertility, mortality and population size. Migration was set to zero due to a lack of available data on migration between states. However the National Population Bureau projections of growth reflect the migration between states for the years 2006–2013.

HIV prevalence data were available in Nigeria for each state from four or five ANC sites from 2003 through 2010. A number of sites, mostly urban sites, also had historical surveillance data from the 1990s. Survey data from the National HIV/AIDS Reproductive Health Surveys in 2007 and 2012 provided HIV prevalence for each state (Supplementary table 1, <http://links.lww.com/QAD/A577>). The 95% confidence bounds on the survey results were very wide in most states. The 2012 household survey interviewed a total of 31 235 individual respondents and the 2007 household survey interviewed a total 11 521 respondents.

Finally, programmatic data are required for each state to determine ART and PMTCT coverage. The number of people receiving ART and PMTCT were not available by state before 2012. To estimate the number of people receiving antiretrovirals for each state before 2012, the distribution of persons (separately for adults, children and pregnant women) receiving antiretrovirals from 2012 was used to distribute the national value to the states in previous years.

Prevalence curve fitting

Three prevalence fitting models are available in Spectrum. The two used for this analysis are described here. The specific descriptions of the models are explained elsewhere [13]. Briefly, the R-Trend model allows the force of infection to change over time based on existing evidence of potential values of the force of infection and other parameters from 62 well documented epidemics. The EPP Classic model provides more structure to the shape of the epidemic curve by assuming a set force of infection over time while the structure of the curve is determined by four parameters. The four parameters include the year the epidemic started, the force of infection which describes how quickly the prevalence trend will rise, the peak prevalence, and the rate at which prevalence declines over time.

The users chose which model to use to fit the prevalence curve based on the amount of prevalence data available.

EPP Classic is used for developing an epidemic curve when there is sparse data (defined loosely as three or fewer sites over three different time periods). EPP Classic was used to fit the HIV prevalence curves for all of the state files. R-Trend is used if there are more than 50 sites over more than 10 years of reporting. R-Trend was used to fit the urban and rural HIV prevalence curves where there were 86 and 74 sites respectively over 4–9 years. R-Spline, the third model in the software, is used for the remaining situations.

Spectrum calculates the uncertainty around the variables produced by using Monte Carlo techniques. The uncertainty calculation for each state is based on two factors: the prevalence data used to estimate the epidemic curve and the assumptions used for the default values in the model. In calculating the aggregate uncertainty for all state files, we assume that uncertainty around the prevalence and incidence trends is uncorrelated across states but that uncertainty around epidemic parameters, such as progression and mortality rates is perfectly correlated across states.

Spectrum software version 5.04 was used for this analysis.

Development of national and sub-national estimates

We compared the aggregated sub-national results against the urban/rural results. The aggregated sub-national results are calculated using Spectrum's aggregate command which simply adds up count variable and calculates any rates (i.e. incidence, prevalence) based on the count variables and the population in each state. As an additional comparison, we re-created the urban/rural model using EPP Classic to determine whether the difference was due to the model selection or using more specific epidemic zones.

Results

As would be expected, the levels and trends of HIV incidence, prevalence, and mortality varied by state in Nigeria. Whereas most states have fairly stable trends in HIV incidence, incidence doubled in Bayelsa and Abia between 2005 and 2013 [from 0.18% (0.10–0.40%) to 0.46% (0.23–0.84%) in Bayelsa and 0.29% (0.16–0.63%) to 0.62% (0.28–1.1%) in Abia]. At the same time, HIV incidence has dropped by more than 50% in Kebbi and Bauchi [from 0.02% (0–0.12%) to 0.01% (0–0.07%) in Kebbi and 0.12% (0.03–0.24%) to 0.03% (0–0.41%) in Bauchi] (see Fig. 1).

Aggregating the state results to form national estimates, we compared the national results for the two methods. There were substantial variations between the aggregated state results and the urban/rural results. HIV incidence (among adults 15–49) was stable with only a 6% decline between 2005 and 2013 in the state-aggregated results.

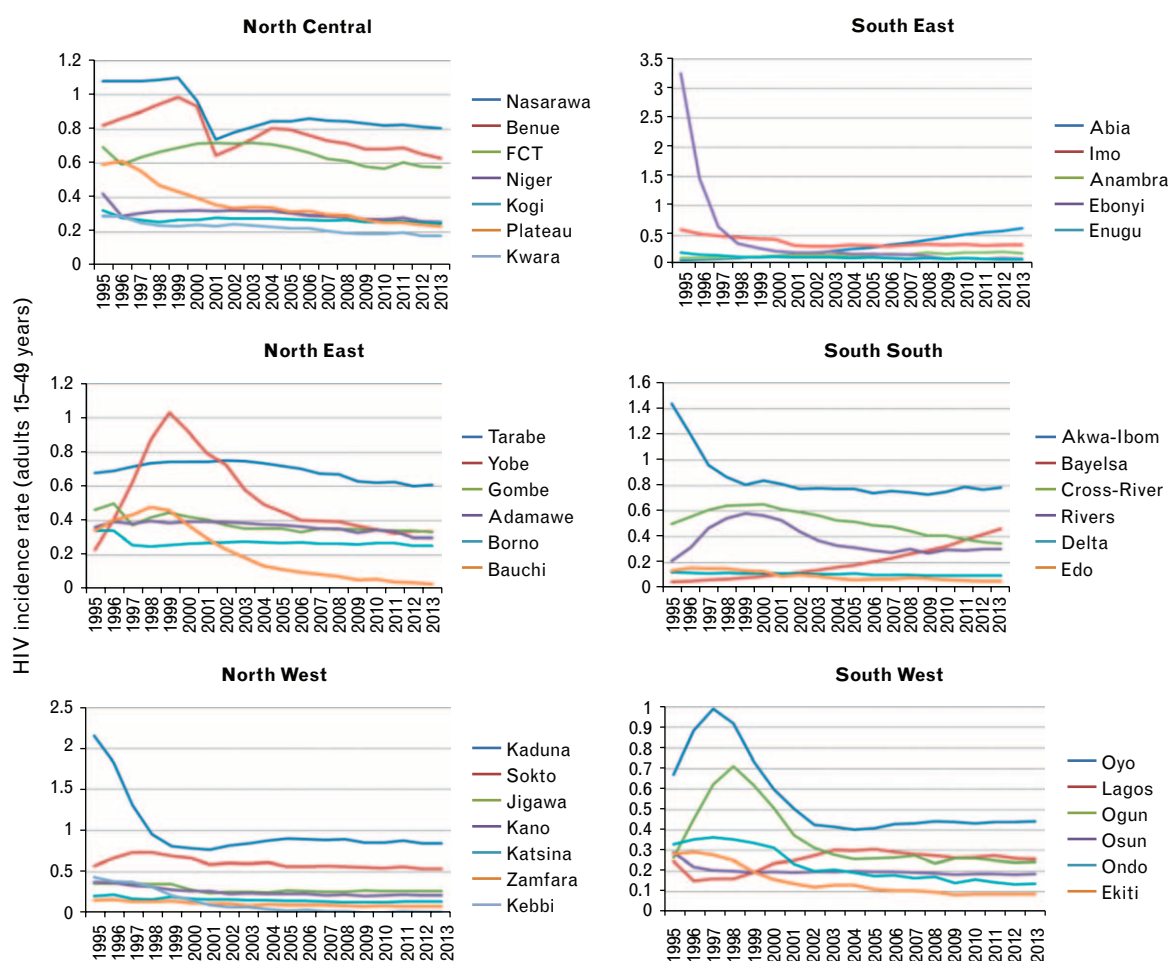


Fig. 1. HIV incidence rate (adults 15–49 years) from the state models, by zone, Nigeria 1995–2013.

HIV incidence declined by 50% over the same time in the urban/rural file.

The selection of the prevalence fitting model had an important impact on the shape of the incidence curve in

EPP. After refitting the urban/rural curves using EPP Classic, the model suggested HIV incidence declined by 8% between 2005 and 2013 – virtually the same decline as the aggregated state files. This suggests that the difference in the trend was primarily due to the model selection.

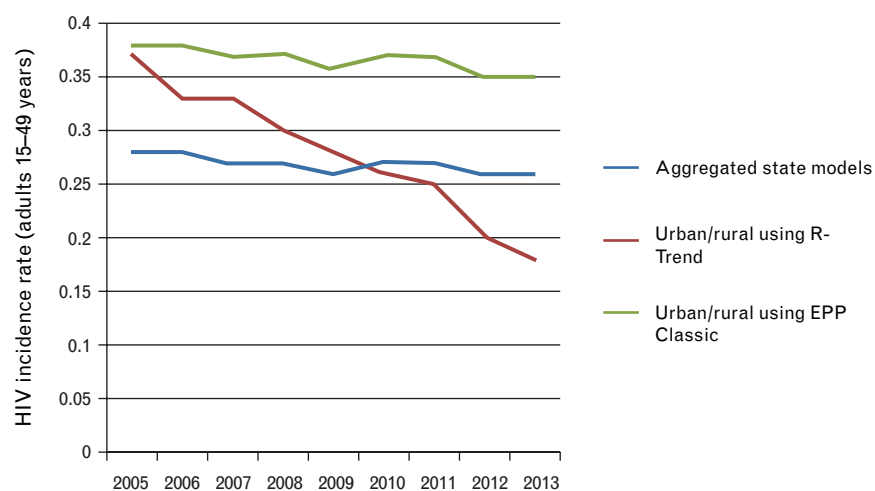


Fig. 2. HIV incidence rate (adults 15–49 years) urban/rural model using R-trend, urban/rural model using EPP classic, and aggregated state models, 2005–2013.

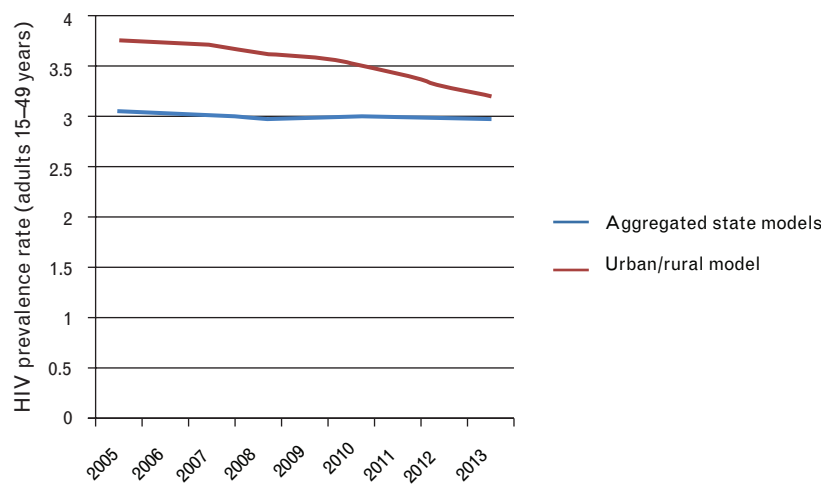


Fig. 3. HIV prevalence (adults 15–49 years), urban/rural model versus aggregated state models, 2005–2013.

Figure 2 shows the comparison of HIV incidence in the two methods and the urban/rural fit using EPP Classic.

The results for the year 2013 also show differences. The estimated adult incidence rates were different in 2013 at 0.3% (0.17–0.49%) in the state-aggregated file and 0.21% (0.17–0.26%) in the national file, although the large uncertainty bounds overlap. Adult HIV prevalence also showed similar trends, but the value for 2013 was slightly higher in the aggregated state files [3.0% (2.0–4.5%) compared to 3.2% (3.0–3.5%) in the urban/rural file] (see Fig. 3). AIDS deaths show similar trends over time between the models; however, the magnitude is slightly higher in the national file: 190 000 (110 000–320 000) versus 210 000 (190 000–240 000), for the year 2013 (see Fig. 4).

The total population of Nigeria was 4% higher in the aggregated files compared with the national file. This is a result of using population growth values provided by two different sources (the National Population Bureau

provided data on the growth rate from 2006 to 2013, whereas data from the United Nations Population Division were used for projections from 2006 to 2013 for the urban/rural file).

For each of the variables described above, the uncertainty around the aggregated state results are considerably larger than the urban/rural results because of the smaller number of surveillance sites in the state files and the smaller survey sample sizes for the states. Hence the need to exercise caution in making inferences on respective HIV trends at the state level.

Estimated HIV prevalence curves for urban areas in Nigeria compared to an example from the state of Kaduna (state with the highest number of people living with HIV) are shown in Fig. 5. In Kaduna, there are five ANC sites reflecting both urban and rural areas. The urban curve shows a cloud of ANC sites (green dots) from which it is difficult to discern a pattern. The Kaduna state ANC

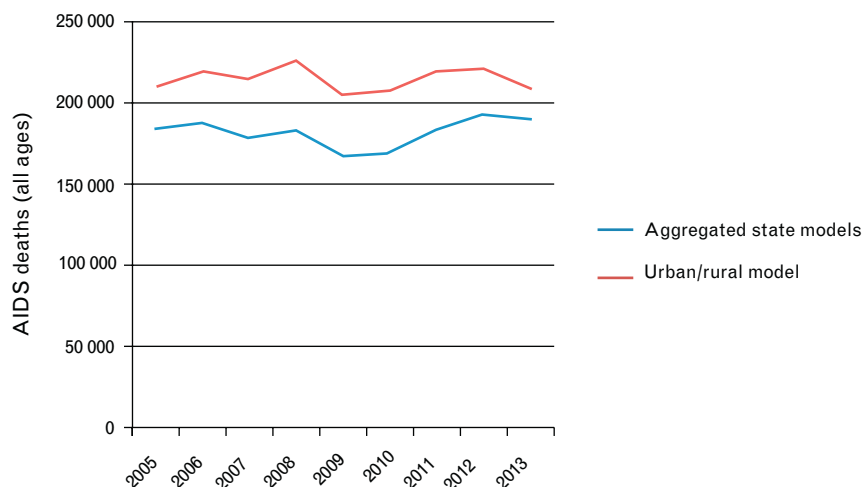


Fig. 4. Annual number of AIDS deaths, Nigeria national model and aggregated state models, 2005–2013.

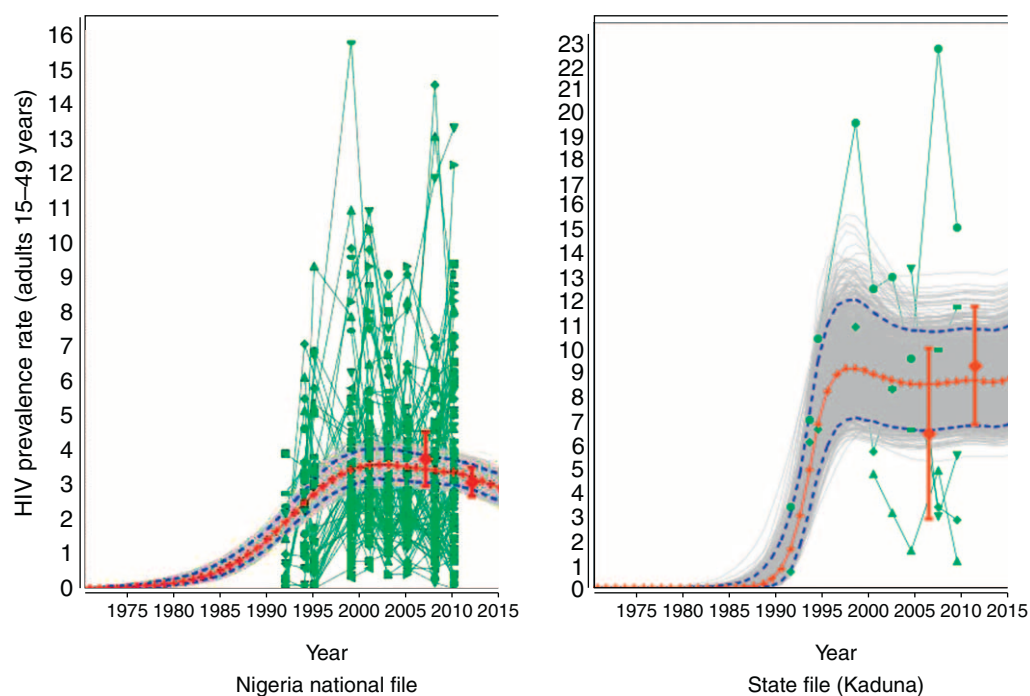


Fig. 5. HIV prevalence trends based on antenatal clinic and household survey data, Nigeria urban areas and Kaduna state. The green points represent HIV prevalence measures from antenatal clinic sites. The green lines connect the data from consistent sites. The red vertical lines identify point estimate and the standard errors for the two National HIV/AIDS and Reproductive Health Surveys (2007 and 2012). The grey lines represent the potential curves that could fit the data and the blue dotted lines are the uncertainty bounds around the potential curves. The red line is the annual median value of the grey lines.

prevalence shows quite a bit of variation from year to year and wide uncertainty around the survey data points (red diamond with uncertainty bars).

Discussion

Sub-national estimates of the HIV epidemic are useful to help countries focus their HIV response. The Nigerian state-level estimates provide governors and state programme managers with trends and levels of HIV incidence, HIV prevalence, AIDS-related deaths and other variables for each of the states in Nigeria; data not previously available at state level. However, developing models for smaller geographic areas with fewer data points resulted in important differences in the national results. The smaller sample sizes used for the state-specific estimates resulted in wider uncertainty around the variables.

The amount of prevalence data available to enter into the model influences which prevalence-fitting method is used in Spectrum. In Nigeria, conclusions about the trends in HIV incidence were dependent on the prevalence-fitting model chosen. A previous unpublished analysis comparing the prevalence-fitting models showed that R-Trend had a lower mean average error in the fit between the data and the resulting curve for Nigeria compared to EPP Classic. This analysis of models from 14 generalized epidemic countries led to the UNAIDS

guidance on which prevalence-fitting model to choose. The limited surveillance data at the state level necessitated the use of EPP Classic. Our analysis showed that the choice of the model resulted in important differences in the incidence trends.

There are a number of limitations to this comparison of the national results using an urban/rural model versus the aggregated state models. There is no gold standard against which to compare these results to determine which method is more accurate. The different sources for the population growth in Nigeria over time resulted in slightly different total population values in 2013; ideally this would have been resolved to ensure the analysis provided a simple description of the differences in the two files. As the number of Spectrum files multiplies, the ability to carefully review the files becomes more challenging, leaving the potential for errors in the state Spectrum files. The representativeness of the ANC sites within each state and for urban and rural areas is not known. Finally, the distributions of people receiving antiretroviral medicines (for ART and PMTCT) by state in the years before 2012 were not available and were approximated based on the 2012 distribution. This assumption might affect the accuracy of the state-specific mortality and incidence trends.

Managers in various states of Nigeria have keenly followed the process of generating state-level HIV

estimates and are eager to use the outputs for their respective strategic operation plans for PMTCT and ART. Similarly, outputs were used to help determine resource needs and inform a detailed technical gap analysis and programmatic target setting for Nigeria at all levels. At the federal level, the outputs have played a pivotal role in state prioritization for funding and technical support by the major development partners. The government has tangible information from which to make sound and evidence-based decisions on the investments towards bridging the funding and technical gaps.

Sub-national estimates can provide programme managers with the tools to better plan, measure and understand the impact of their HIV epidemic. However, careful consideration of whether the appropriate surveillance data are available (within each sub-national entity and over time) and the appropriate selection of the prevalence fitting model is needed. Sub-national data provide an important change in perspective for national and state based planners.

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MM developed the analysis concept and drafted the manuscript, MN, DO, MCM lead the development of national and state Spectrum files and helped develop the manuscript, MO and JS provided critical review of the manuscript and JS developed the Spectrum software.

Conflicts of interest

There are no conflicts of interest.

References

1. UNAIDS. Location: connecting people faster to HIV services. Geneva; 2013.
2. UNAIDS. The Gap Report. Joint United Nations Programme on HIV/AIDS. Geneva, Switzerland 2014.
3. Prudden HJ, Watts CH, Vickerman P, Bobrova N, Heise L, Ogungbemi MK, *et al.* **Can the UNAIDS modes of transmission model be improved? A comparison of the original and revised model projections using data from a setting in west Africa.** *AIDS* 2013; **27**:2623–2635.
4. Federal Ministry of Health N. National AIDS Spending Assessment (NASA) Report. 2012.
5. Carael M. **Urban-rural difference in HIV/STD and sexual behaviour.** In: Herdt G. editor. *Sexual cultures and migration in the era of AIDS* Oxford: Clarendon Press, Oxford University Press; 1997. pp. 107–126.
6. Carael M, Holmes KK. **Dynamics of HIV epidemics in sub-Saharan Africa: introduction.** *AIDS* 2001; **15** (Suppl 4): S1–S4.
7. UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. Guidelines for conducting HIV sentinel serosurveys among pregnant women and other groups Geneva: World Health Organization; 2003.
8. Ministry of Health Botswana. 2011 Botswana Second Generation HIV/AIDS Antenatal Sentinel Surveillance Technical Report. Gaborone; 2012.
9. Ministry of Health and Social Services Namibia. Report on the 2012 National HIV Sentinel Survey. Windhoek: Ministry of Health and Social Services; 2013.
10. Federal Republic of Nigeria. National HIV and AIDS and Reproductive Health Survey 2012. Abuja: Federal Ministry of Health; 2013.
11. Federal Ministry of Health N. National HIV Sero-prevalence Sentinel Survey Among Pregnant Women Attending Antenatal Clinics in Nigeria. Abuja, Nigeria: Federal Ministry of Health; 2012.
12. Stover J. AIM: a computer program for making HIV/AIDS projections and examining the demographic and social impacts of AIDS. Glastonbury, CT: Futures Institute; 2009.
13. Brown T, Bao L, Eaton JW, Hogan DR, Mahy M, Marsh K, *et al.* **Improvements in prevalence trend fitting and incidence estimation in EPP 2013.** *AIDS* 2014; **28** (Suppl 4):S415–S425.